Journal of Surgical Oncology 64:218–221 (1997)

Perianal Mucinous Adenocarcinoma

THOMAS ANTHONY, MD,[1,2]* CLIFFORD SIMMANG, MD,[1] EDWARD L. LEE, MD,[2] AND RICHARD H. TURNAGE, MD
[1]University of Texas Southwestern Medical Center, Dallas, Texas
[2]Veterans Affairs Medical Center, Dallas, Texas

Background: Perianal mucinous adenocarcinoma is a rare variant of anal canal epithelioid tumors. Our objective in this report is to examine the clinical features, pathology, treatment, and outcome for patients with perianal mucinous adenocarcinoma.
Methods: A retrospective review identified four patients with histologically proven perianal mucinous adenocarcinoma. The medical records of these patients were reviewed for presentation, therapy, and outcome.
Results: Pain and bleeding were present in all cases. In three of four patients, chronic perirectal disease was present, including two abscesses and one fistula. All patients had extensive local disease at presentation. One patient presented with bilateral inguinal nodal metastases. Two patients received neoadjuvant chemotherapy and radiation, with a third patient receiving radiation alone. Two of these three patients underwent abdominoperineal resection. Three patients subsequently died (all of progression and/or recurrence) 2–48 months after diagnosis. The fourth patient (who was treated with chemotherapy and radiation followed by abdominoperineal resection) is alive and disease free at 12 months.
Conclusions: Perianal mucinous adenocarcinoma is a rare disease with a poor prognosis, mostly due to its advanced nature at the time of diagnosis. Chemoradiation followed by surgery may improve outcome in selected individuals. *J. Surg. Oncol. 64:218–221*

KEY WORDS: anal adenocarcinoma; prognosis; treatment

INTRODUCTION

Anal carcinoma represents ~1% of all tumors of the gastrointestinal (GI) tract. Adenocarcinoma of the anal region is a rare histologic variant of more common tumors in this location; the vast majority of cancers in this region are squamous cell or squamous variants. In most large series of carcinomas of the anal canal, <10% of cases are adenocarcinomas [1–4]. A recent survey of the American Society of Colon and Rectal Surgeons identified only 52 cases of anal gland adenocarcinoma among patients treated by members of this society [5]. Because of the infrequency with which this tumor is encountered, physicians are generally unaware of the significance of this histology in determining therapeutic outcome. The purpose of this report is to discuss our own experience with this rare cancer and to highlight the clinical features, pathology, treatment, and outcome for patients with perianal mucinous adenocarcinoma.

MATERIALS AND METHODS

Patients

A retrospective review of the pathology department's computerized database from January 1, 1985 to December 31, 1995, was undertaken to search for anal adenocarcinoma. The information obtained was then cross-referenced with the Dallas Veterans Affairs Medical Center Cancer Registry database over the same period. Four patients were identified, and their complete pathologic and clinical records were reviewed. Gross and permanent histology were reviewed by a single senior pathologist (EL). A detailed review of each patient's medical record was undertaken, concentrating on demographics, presentation, therapy, and outcome. We classi-

*Correspondence to: Thomas Anthony, M.D., 5323 Harry Hines Blvd., Dallas, TX 75235-9031. Fax: (214) 648-7965
Accepted 28 November 1996

TABLE I. Perianal Mucinous Adenocarcinoma: Summary of Patient Presentation, Therapy, and Outcome

Patient #	Age	Presentation	Therapy[a]	Survival
1	68	Perirectal abscess: 12 cm area of induration	None	Died at 2 months
2	74	Fistula–In–Ano with 7 cm induration	5,000 RAD → APR	Died at 48 months
3	61	Large (6 cm) Exophytic mass bilateral inguinal adenopathy	5 FU/Mito C × 2 + 5,400 RAD → APR	Alive at 12 months
4	50	20-year history of perirectal disease: 9 cm indurated area with central ulcer	FAM × 2 → 7,620 RAD	Died at 14 months

[a]APR = abdominoperineal resection, 5 FU = 5-fluorouracil, Mito C = mitomycin C, FAM = 5-fluorouracil, Adriamycin and mitomycin C.

fied these patients' tumors by using the 1976 World Health Organization (WHO) classification of anal adenocarcinoma, which recognizes three variants: rectal, anorectal fistula, and anal gland adenocarcinoma [6].

RESULTS

Clinical Features

All four of the patients identified in this review were males ranging from 50 to 74 years of age (mean age = 63). Three of four individuals had a history of chronic perirectal abscess or fistula. All four patients presented with pain and bleeding. On examination, three patients had large (7–12 cm) indurated perirectal areas with surrounding erythema. In two of these three individuals, there was an associated abscess. The third patient had a well-defined fistulous tract with surrounding inflammation, induration, and erythema but no purulence. The fourth patient had a large exophytic mass (~6 cm in diameter) extending outward from his perineum. This mass prevented digital rectal examination. On all three patients in whom digital rectal examination and endoscopic evaluation were possible, there was no sign of mucosal involvement. The diagnosis was made in each case in the operating suite with examination under anesthesia, incision, and drainage of areas of fluctuance and biopsy of suspicious areas. One patient presented with bilateral inguinal lymph node involvement, which was confirmed by fine-needle aspiration cytology. Using the WHO classification system, three patients had anorectal fistula type adenocarcinomas and one patient had an anal gland type adenocarcinoma. Histologically, each patient's tumor was confirmed to be a mucin producing adenocarcinoma.

Therapy and Outcome

In one patient, no therapy was given due to an extensive array of medical comorbid factors. This patient survived 2 months from the time of diagnosis. Because of the clinically large size of the tumor in each of the remaining cases, these patients all underwent neoadjuvant therapy in an attempt to downstage the tumor prior to surgical resection. One patient was treated with 5,000 cGy of external beam radiation, with minimal decrease in tumor size. This radiation treatment was followed by abdominoperineal resection, after which the patient lived 48 months. He eventually developed widespread metastatic disease, including bilateral inguinal, celiac nodal, and pulmonary metastases. A second patient, who presented with bilateral inguinal nodal disease and a large primary tumor, was treated with two cycles of 5-fluorouracil and mitomycin C with 5,400 cGy of external beam radiation, which resulted in a 50% objective reduction in tumor volume and a complete response in his inguinal nodes. An abdominoperineal resection was subsequently performed. This patient is alive and free of disease at 12 months follow-up after surgical resection. The final patient was treated with two cycles of 5-fluorouracil, adriamycin, and mitomycin-C, followed by 7,620 cGy of external beam radiation. There was no response in the tumor, which was considered unresectable because of its large size. This patient died with metastatic inguinal and pulmonary disease ~14 months after diagnosis. Treatment and outcome are summarized in Table I.

DISCUSSION

The anal canal represents the short anatomic transition zone (~4 cm in length) between perianal squamous mucosa and the columnar epithelial lining of the rectum. This region may be further subdivided histologically into a proximal columnar zone that more distally gives way to a transitional zone formed of mixed columnar, cuboidal, anal glandular, basaloid, and squamous components. Finally, more distally still, the transition zone gives way to an entirely squamous epithelium at the dentate line. The histologic complexity of this region accounts for the wide variety of tumors occurring in this area including perianal mucinous adenocarcinoma.

Since Rosser [7], in 1934, first proposed an anal duct or gland origin of these neoplasms, there has been considerable controversy concerning which tumors should be considered distal rectal cancers and which tumors would be more properly treated as anal canal adenocarcinomas. The broadest definition of anal adenocarcinoma is attributed to Zimberg and Kay [8], who suggested that anal canal adenocarcinoma with little to no mucosal involvement compared with submucosal or lateral involvement should be considered anal duct in origin. At the other end of the spectrum, the strictest criteria have been

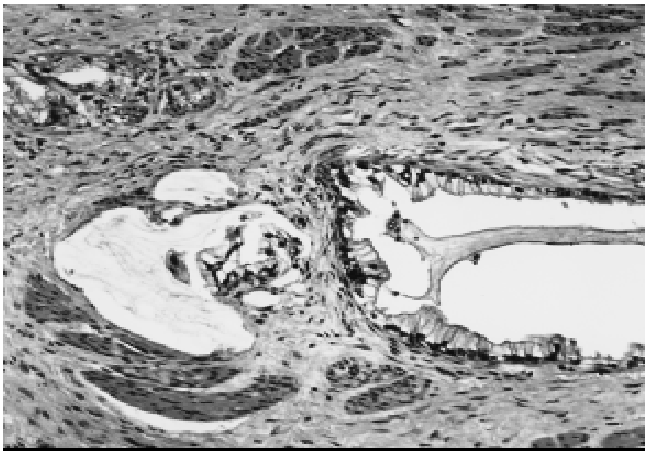

Fig. 1. Perianal mucinous adenocarcinoma showing typical mucin filled epithelial lined cystic spaces. The lakes of mucin and the bland epithelial cells may be misinterpreted as benign.

put forth by Fenger and Morson [9] and include: (1) origin at site where anal glands are present, (2) exclusion of mucosal origin, anal fistulas, gut duplications, and metastatic deposits, (3) transition from normal anal gland to carcinoma preferably with interposed dysplastic epithelium, and (4) a distinctive microscopic picture consistent with an anal gland origin. To avoid this controversy, most authors have adopted the WHO criteria to define these tumors. This scheme recognizes three variants: rectal, anorectal fistula, and anal glandular types. The latter two types are also commonly referred to as perianal mucinous adenocarcinomas, a term that highlights the histologic tendency of tumors from this area to be composed of cystic spaces filled with mucin and lined by malignant epithelial cells (Fig. 1). In our experience, these tumors all have been quite large at the time of presentation and have obliterated much of the normal anatomy, making it impossible to say with certainty what the precise origin was of these tumors. In all four cases there was no appreciable mucosal involvement in either the distal rectum or the anal canal itself. A history of chronic perirectal disease was obtained in three of our four patients (in one case being present for >20 years). At the time of presentation, these patients had what appeared to be continuations of that disease process, with tumor found during incision and drainage of perirectal abscesses in two patients and during fistulotomy in the third patient. We classified these patients as having anorectal fistula type anal adenocarcinomas. Our fourth patient had a large exophytic mass extending outward from his perineum. Histologically, we were not able to identify any mucosal point of origin, and the tumor appeared to begin in the region where the anal glands could be expected. However, we were unable to identify a point of transition from normal anal glandular epithelium to malignancy. Nevertheless, we feel that, based on the histologic and anatomic evidence, this patient's tumor was best classified as an anal gland adenocarcinoma.

As was the case with our patients, the majority of patients in previous reports have had extensive disease at the time of presentation, making successful treatment difficult [10]. The standard treatment option for these patients has been surgical. The Miles' abdominoperineal resection is the most frequently employed operation [3,5,11,12]. The prognosis for anal adenocarcinoma is quite poor despite this aggressive surgical therapy. Five-year survival with standard surgical approaches has been <20% in most series (Table II). This low survival rate is in marked contrast to other epithelioid cancers of the anal canal, where 5-year survival rates of between 64 and 90% have been reported [13]. The overall poor survival for perianal adenocarcinoma most likely reflects the advanced stage of disease presentation of these tumors.

Since the symptoms of anal adenocarcinoma are similar to perirectal disease in general and they often develop against a background of chronic perirectal disease (as in our cases), patients will frequently experience prolonged periods of symptoms prior to diagnosis and treatment. Additionally, physicians frequently misdiagnose these patients as having other forms of perirectal pathology based on their past medical histories leading to further delay in diagnosis. Several authors have emphasized the necessity of a high index of clinical suspicion in any elderly patient presenting with perirectal abscess or in patients with long-standing perirectal disease [11,12,15,16]. Certainly in our own series, this may have resulted in an earlier diagnosis with more favorable outcome.

A second route toward improving the outcome of patients with anal adenocarcinoma may be through the of use of neoadjuvant therapy. The same therapeutic strategy that has so successfully reduced the mortality from the more common forms of epithelioid anal canal carcinomas has not been widely applied to adenocarcinomas arising in this region. Nelson et al. [15] reported the first patients with anal adenocarcinoma treated under a Nigro or Wayne State type protocol (mitomycin C 10 mg per meter squared day 1, 5 fluorouracil 750–1,000 mg per meter squared continuous infusion days 1–4 and 29–32, and 3,000–4,500 cGy of external beam radiation in 200 cGy fractions followed by surgical resection). Nelson [15] reported a good response in seven of the nine patients treated. In our own limited experience with combined neoadjuvant chemotherapy and radiation, we have had mixed results, one patient having no response, and one patient having a complete response in his inguinal nodes and a partial response at the primary tumor site. We believe that this approach warrants further study, however, the infrequency with which this disease entity is encountered will make assessment of the efficacy of this approach difficult.

TABLE II. Perianal Mucinous Adenocarcinoma: Summary of Selective Review of the Literature

Ref #	Author	# of Pts	Location	Therapy[a]	Survival
10	Jensen	21	Anal duct origin	Local excision = 3 APR = 3 Colostomy = 9 Radiotherapy = 2	5-year 4.8% 20/21 died within 18 mo.
11	Basik	10	4 Rectal 2 Anal duct 1 Anorectal fistula 3 Unclassified	APR = 7 Proctectomy/vulvectomy = 1 Local excision = 2	7/10 recurred median 28-mo survival
3	Mercini	9	Anal gland	NA	17% 5-year survival
14	Beahrs	6	Perianal = 3 Anal canal = 3	''Main treatment'' APR	16% 5-year survival

APR = abdominoperineal resection; NA = not available.

CONCLUSIONS

Adenocarcinomas are rare cancers of the perianal region. They frequently present at a late stage through patient neglect and physician misdiagnosis. The traditional therapy for these individuals has been abdominoperineal resection. Despite this aggressive operative management, 5-year survival is generally <20%. A heightened clinical suspicion (especially in the elderly or in patients with chronic perirectal disease), resulting in earlier diagnosis and the use of multimodality therapy consisting of combined neoadjuvant chemotherapy and radiation prior to definitive surgery may result in improved survival for patients with anal adenocarcinoma.

REFERENCES

1. Cola B, Ismail I, Montanari-Reggianni F, et al: Le cancer de l'anus: role actuel de la chirurgie. Chirurgie 1990;116:89–97.
2. Welch JP, Malt RA: Appraisal of the treatment of carcinoma of the anus and anal canal. Surg Gynecol Obstet 1977;145:837–847.
3. Merlini M, Eckert P: Malignant tumors of the anus. Am J Surg 1985;150:370–372.
4. Cabrera A, Tsukada Y, Pickren JW: Adenocarcinomas of the anal canal and perineal tissues. Ann Surg 1966;164:152–156.
5. Abel ME, Chiu YSY, Russel TR, Volpe PA: Adenocarcinoma of the anal glands: results of a survey. Dis Colon Rectum 1993;36: 383–387.
6. Morson BC, Sobin LH: ''Histologic typing of intestinal tumors.'' Geneva: WHO, 1976;62–64.
7. Rosser C: The relation of fistula in ano to cancer of the anal canal. Trans Am Proc Soc 1934;35:65–71.
8. Zimberg YH, Kay S: Anorectal carcinomas of extra-mucosal origin. Ann Surg 1957;145:344–354.
9. Fenger C, Morson BL: Anal duct carcinoma. Dis Colon Rectum 1989;32:355–357.
10. Jensen SL, Shokouh-Amiri MH, Hagen K, Hvring H, Vagn-Neilsen O: Adenocarcinoma of the anal ducts: a series of 21 cases. Dis Colon Rectum 1988;31:268–272.
11. Basik M, Rodriguez-Bigas MA, Penetrante R, Petrelli NJ: Prognosis and recurrence patterns of anal adenocarcinoma. Am J Surg 1995;169:233–237.
12. Nelson RL, Prasad ML, Abcarian H: Anal carcinoma presenting as a perirectal abscess or fistula. Arch Surg 1985;120:632–635.
13. Shank B, Cohen AM, Kelsen D: Cancer of the anal region. In Devita VT, Helman S, Rosenberg SA (eds): ''Cancer: principles and practice of oncology.'' Philadelphia: Lippincott, 1993:1006–1023.
14. Beahrs OH, Wilson SM: Carcinoma of the anus. Ann Surg 1976; 184:422–428.
15. Tarazi R, Nelson RL: Anal adenocarcinoma: a comprehensive review. Semin Surg Oncol 1994;10:235–240.
16. Prioleay PG, Auen MS Jr, Roberts T: Perianal mucinous adenocarcinoma. Cancer 1977;39:1295–1299.